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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,458	09/10/2003	Gary W. Pace	8703-510	7151

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,458	PACE ET AL.	
	Examiner	Art Unit	
	Ernst V. Arnold	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4,13-16 and 20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-12, 17-19, 24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-25 are pending. Claims 4, 13-16 and 20-23 are withdrawn from consideration. Claims 24 and 25 are new. Claims 1-3, 5-12, 17-19, 24 and 25 are under examination. Applicant's amendment necessitated a new ground of rejection. This Action is FINAL.

Comment: Applicant asserts that the drawings will corrected at the time of allowance but until that time the drawings shall remain objected.

Drawings

The drawings are objected to because the legend on the left side of the graph is not legible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner,

the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7-9, 12, 17-19, 24 and 25 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Ross et al. (Pain 2000, 84, 421-428).

Ross et al. disclose methods of administering sub-analgesic amounts of morphine and oxycodone, in the forms of the hydrochloride salt, to adult rats via intraperitoneal and subcutaneous dosing (Abstract, page 422, 2.2 drugs; 2.4 dosing regimens). Marked antinociceptive synergy was observed following simultaneous administration of sub-antinociceptive doses of oxycodone and morphine (Page 423, 3. results and page 426, 4. Discussion). It is the Examiner's position that even rats are at risk for respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea. Thus the method disclosed by Ross et al. intrinsically reduces the risk associated with the administration of opioid analgesics in patients and reads on claims 1-3, 7, 12 and 17-19. Ross et al. teach dosing ratios of oxycodone to morphine of 25%:75%; 50%:50%or 75%:50% relative to the ED_{50} doses of either morphine or

oxycodone as determined in their experiments thus reading on instant claims 8 and 9 (Page 423, 2.4.4 subcutaneous dosing and page 425, Figures 2 and 3).

Please note that the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics such as the combined mass of morphine and oxycodone is about 50% of the mass of morphine alone required to achieve the same analgesic effect and wherein the combined mass of morphine and oxycodone is about 75% of the mass of oxycodone alone required to achieve an analgesic effect. When as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Response to arguments:

Applicant asserts that Ross et al. do not contemplate the effect on respiratory depression and the same level of analgesic synergy would also produce a similar level of side effects. Applicant asserts that the mixed opioid composition of the instant invention provides an unexpected benefit over the prior art reference. The Examiner cannot agree. The claims are directed to reducing the risk associated with the administration of opioid analgesics. The risk, though not defined in the claim, is ostensibly respiratory depression. Administration of less opioid reduces at least that risk. Applicant asserts that the prior art does not teach the ratio of opioids required to produce both analgesia and a reduction in respiratory depression. The Examiner cannot

agree. The ratio of components taught in the art do embrace the instant ratios of oxycodone to morphine from about 2:3 to about 2:1. As stated above, Ross et al. teach dosing ratios of oxycodone to morphine of 25%:75%; 50%:50%or 75%:50% relative to the ED_{50} doses of either morphine or oxycodone as determined in their experiments thus reading on instant claims 8 and 9 (Page 423, 2.4.4 subcutaneous dosing and page 425, Figures 2 and 3). Applicant calculates relative mass ratios from 1:9 to 1:1 in the Ross et al. reference, which embrace the instant range of about 2:3 to about 2:1. Besides the fact that instant claim 1 does not recite any specific ratio of opioid agonists, clearly at least the ratio of 1:1 (2:2) is anticipated by Ross et al. Ross et al. do not comment on any signs of respiratory depression in the mice. However, Ross et al. report that co-administration of sub-antinociceptive doses of oxycodone plus morphine produced unexpected antinociceptive synergy with ***a reduced incidence of CNS side effects*** (page 426, Discussion). Thus contrary to Applicant's assertion that the side effects would be commensurate in intensity with the analgesia produced, Ross et al. report reduced side effects.

Applicants arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

Claims 1-3, 5, 7-12, 17-19, 24 and 25 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (WO 97/14438).

Smith et al. disclose methods of producing analgesia in humans and lower animals which comprising administering sub-analgesic dosages of morphine and

oxycodone and their pharmaceutically acceptable salts (Claim 23-25 and 28). Smith et al. also disclose hydromorphone (Claim 24 and 27). The route of administration can be subcutaneous, intravenous, intramuscular, buccal, sublingual, oral or rectal, for example and reads on claim 10 and 12 (Claims 30-35 and 44, for example). The analgesic composition can be administered in oral slow- or controlled release dosage form and thus reads on instant claim 11 (claims 44 and 46). It is the Examiner's position, in the absence of evidence to the contrary, that Smith et al. make the distinction between immediate release oral dosing and sustained release oral dosing in claims 44 and 46 and thus reads on instant claim 10. Since any patient is at risk for a diagnosed or undiagnosed respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea, then the method of reducing the risk associated with the administration of opioid analgesics is inherent in the method of Smith et al. thus reading on instant claims 17-19. Smith et al. disclose a wide range of dosing regimens, which the Examiner interprets to read on instant claims 8, 9, 24 and 25 (Claims 25-43). Thus, instant claims 1-3, 5, 7-12, and 17-19, 24 and 25 are anticipated by Smith et al.

Please note that the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics such as the combined mass of morphine and oxycodone is about 50% of the mass of morphine alone required to achieve the same analgesic effect and wherein the combined mass of morphine and oxycodone is about 75% of the mass of oxycodone alone required to achieve an analgesic effect. When as here, the prior art appears to contain the exact

same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Response to arguments:

Applicant asserts that Smith et al. do not disclose a reduction in side effects and the disclosed ratio of opioids (1:9 to 1:1 of oxycodone:morphine) do not anticipate the instantly claimed ranges. The Examiner cannot agree. As stated above, the claims are directed to reducing the risk associated with the administration of opioid analgesics. The risk, though not defined in the claim, is ostensibly respiratory depression. Administration of less opioid reduces at least that risk. Applicant asserts that the prior art does not teach the ratio of opioids required to produce both analgesia and a reduction in respiratory depression. The Examiner cannot agree. The ratio of components taught in the art do embrace the instant ratios of oxycodone to morphine from about 2:3 to about 2:1 because 1:1 (2:2) is embraced by about 2:3 to about 2:1.

Claim Rejections - 35 USC § 102

Claims 1-3, 5, 7-12, 17-19, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (US 6,310,072).

Smith et al. disclose

> **72**. A method for producing analgesia in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising a sub-analgesic dosage of a μ-opioid agonist selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil and hydromorphone, or a pharmaceutically acceptable salt thereof, and a sub-analgesic dosage of oxycodone which is a κ_2-opioid agonist or a pharmaceutically acceptable salt thereof.
>
> **73**. A method as claimed in claim **72** wherein the μ-opioid agonist is in the form of a pharmaceutically acceptable salt.
>
> **74**. A method as claimed in claim **72** wherein the μ-opioid agonist is morphine.

Since any patient is at risk for a diagnosed or undiagnosed respiratory illness such as sleep apnea which can be central, obstructive or mixed sleep apnea, then the method of reducing the risk associated with the administration of opioid analgesics is inherent in the method of Smith et al. thus reading on instant claims 1-3, 5, 7 and 17-19.

Smith et al. disclose

> mg/kg and about 5 mg/kg every three to six hours.
>
> **143**. A method as claimed in claim **72** wherein the mode of administering the composition is selected from the group consisting of oral, rectal, parenteral, sublingual, buccal, intrathecal, epidural, intravenous, intra-articular, intramuscular, intradermal, subcutaneous, inhalational, intraocular, intraperitoneal, intracerebroventricular and transdermal.

thus reading on instant claim 12.

Smith et al. disclose various administration routes and controlled-release dosage forms reading on instant claim 11 (see claim 155). It is the Examiner's position, in the

absence of evidence to the contrary, that Smith et al. make the distinction between immediate release oral dosing and sustained release oral dosing and thus reads on instant claim 10.

Smith et al. disclose a wide range of dosages in claims 72-145 which would read upon instant claims 8 and 9. Please note that the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics such as the combined mass of morphine and oxycodone is about 50% of the mass of morphine alone required to achieve the same analgesic effect and wherein the combined mass of morphine and oxycodone is about 75% of the mass of oxycodone alone required to achieve an analgesic effect. When as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Response to arguments:

The same argument is applicable here as above since Smith et al. (WO '438) is the foreign counterpart to Smith et al. (US '072) and they share a common disclosure and the arguments are the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5-12, 17-19, 24 and 25 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 97/14438).

Applicant claims a method for reducing the risk associated with the administration of opioid analgesics in patients.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The reference of Smith et al. (WO 97/14438) is described in detail above and that discussion is hereby incorporated by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Smith et al. do not expressly teach a composition with sub-analgesic amounts of oxymorphone.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use sub-analgesic amounts of oxymorphone in the composition of Smith et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because morphine renders obvious other opioids with the same structural backbone to one of ordinary skill in the art and Smith et al. clearly suggest analogs or derivatives of morphine and hydromorphine for use in the method (Claim 24). The amount of opioid to use in the composition is merely routine optimization of the amounts taught by Smith et al. (See claims 25-43).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant asserts that there is no motivation to substitute oxymorphone for morphine in the composition. The Examiner cannot agree. Smith et al. clearly teach derivatives of morphine for use in the composition. Oxymorphone is a derivative of morphine. The motivation to use oxymorphone comes directly from Smith et al.

Applicant's arguments are not persuasive and the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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